UDC 547.94 : 582.572.2

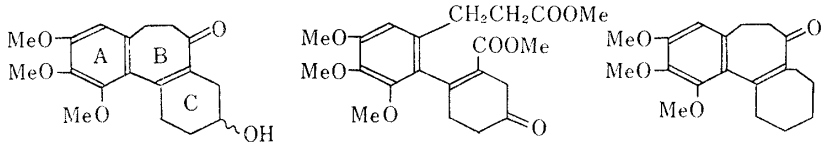
45. Genshun Sunagawa, Takahiro Nakamura, and Jun-ichi Nakazawa : Studies on the Total Synthesis of *dl*-Colchiceine. II.[1] Synthesis of *dl*-Demethoxydeoxyhexahydrocolchiceine.

(*Takamine Laboratory, Sankyo Co., Ltd.*[*1])

As reported in Part I of this series,[1] ring extension of the cyclohexenone ring in methyl 2-[2,3,4-trimethoxy-6-(2-methoxycarbonylethyl)phenyl]-5oxo-1-cyclohexenecarboxylate (II) was attempted but did not materialize during the C-ring extension in 3-hydroxy-9,10,11-trimethoxy-1,2,3,4,6,7-hexahydro-5*H*-dibenzo[*a*, *c*]cycloheptatrien-5-one (I) for the synthesis of colchicine.

Recently, it has become easy to synthesize tropone, either by oxidation of cycloheptatriene[2] or by disproportionation of the ditropyl ether obtained from a tropylium salt.[3] Nozoe and his school also reported the conversion of tropone to tropolone.[4]

Attempt was now made for the synthesis of 1,2,3-trimethoxy-5,6,9,10,11,12-hexahydrobenzo[*a*]heptalen-7(8*H*)-one (III).



(I) (II) (III)

Boekelheide and others[5] had tried to synthesize (III) but gave up due to failure in the Pechmann reaction of 3-methoxy-4,5-diacetoxyhydrocinnamic acid and ethyl 2-oxocycloheptanecarboxylate. Since the Pechmann condensation of 3-methoxy-4,5-dihydroxyhydrocinnamic acid and ethyl 2-oxocycloheptanecarboxylate was also unsuccessful in this laboratory, synthesis of (III) was attempted by the route described in Part I.[1]

The Pechmann condensation of 1-O-methylpyrogallol and ethyl 2-oxocycloheptanecarboxylate gave the coumarin compound in a good yield and derived to 3-methoxy-4-hydroxy-8,9,10,11-tetrahydrobenzo[*b*]cyclohepta[*d*]pyran-6(7*H*)-one (IV), whose infrared spectrum exhibited a new absorption for coumarin CO at 5.92 μ. Allylation of (IV) gave the 4-allyloxy compound (V) which was heated in N,N-dimethylaniline and underwent *para*-Claisen rearrangement to form the alkali-soluble phenol compound (VI), whose infrared spectrum no longer showed the absorption at 12.43 μ for the out-of-plane vibration of adjacent hydrogens but exhibited a new absorption at 11.63 μ for isolated hydrogen and an absorption at 2.88 μ for a phenolic hydroxyl. These spectral evidences indicated that (VI) is 1-allyl compound formed by para rearrangement of the allyl group in (VI). Isomerization of this 1-allyl compound by heating in methanolic potassium hydroxide solution resulted in the shift of the double bond to form 1-propenyl compound (VII) in a good

*1 Nishi-shinagawa, Shinagawa-ku, Tokyo (砂川玄俊, 中村隆洋, 中沢準一).

1) Part I : This Bulletin, **10**, 281 (1962).
2) T. Mukai, T. Tezuka, K. Osaka : Paper presented at the 12th Annual Meeting of the Chemical Society fo Japan, kyoko, 1959; G. Sunagawa, N. Soma, H. Nakao : Paper presented at the Kwanto Local Meeting of the Pharmaceutical Society of Japan, Tokyo, 1959.
3) T. Ikemi, T. Nozoe, H. Sugiyama : Chem. & Ind. (London), **1960**, 932; A.P. Ter Borg, R. van Helden, A.F. Bickel, W. Renold, A.S. Dreiding : Helv. Chim. Acta, **43**, 457 (1960).
4) T. Nozoe, *et al.* : Sci. Repts. Tohoku Univ., Ser. A, **37**, 388 (1953); T. Nozoe, T. Mukai, K. Takase : *Ibid.*, **39**, 164 (1956).
5) V. Boekelheide, F.C. Pennington : J. Am. Chem. Soc., **74**, 1558 (1952).

yield. The formation of (VII) was proved by the disappearance of absorption at 10.96 μ for the allyl group present in the infrared spectrum of the 1-allyl compound (VI). Reaction of 1 mole of ozone with 1-propenyl compound (VII) in the cold resulted in the reaction of the double bond in the side chain alone to form the 1-formyl compound (VIII), whose infrared spectrum showed absorptions for CHO at 6.01 μ and for coumarin CO at 5.85 μ. Knoevenagel reaction of the 1-formyl compound (VIII) and malonic acid gave 1-(2,2-dicarboxyethylene) compound (IX) in a good yield and absorption of one mole of hydrogen by (IX) over palladium-carbon probably resulted in hydrogenation of the double bond in the side chain, as in the reduction of α-carboxy-3-methoxy-6-oxo-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-acrylic acid reported in the preceding paper, without reduction of the coumarin ring, since the reduction product (X) had absorption maxima at 264～268 and 328 mμ in its ultraviolet spectrum.

The infrared spectrum of 3-methoxy-4-hydroxy-6-oxo-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-1-acrylic acid (XI), formed by decarboxylation of the 1-(2,2-dicarboxyethylene) compound (IX), clearly indicated the absorption for *trans*-disubstituted ethylene at 10.25 μ but that of the carboxylic acid (XII) obtained by decarboxylation of (X) by heating it at 180° in a reduced pressure had no absorptions corresponding to them. This showed that (XII) is not a *trans*-disubstituted ethylene compound and, consequently, reduction of 1-(2,2-dicarboxyethylene) compound (IX) resulted in hydrogenation of the side-chain double bond alone, so that the reduction product (X) is 1-(2,2-carboxyethyl) compound and its decarboxylation product is 1-(2-carboxyethyl) compound (XII).

The 1-(2-carboxyethyl) compound (XII) was heated in alkali to open the coumarin ring and concurrent methylation with dimethyl sulfate should give 2-〔6-(2-carboxyethyl)-2,3,4-trimethoxyphenyl〕-1-cycloheptenecarboxylic acid (XIII). The infrared spectrum (in Nujol) of the dicarboxylic acid (XIII) thereby obtained had absorptions at 2.98, 3.7～4.0, 5.73, and 5.95 μ, of which, those at 3.7～4.0 and 5.95 μ may be understood as the hydroxyl and carbonyl in the dicarboxylic acid, but the absorption at 2.98 μ may be that of a phenolic hydroxyl. Therefore, the dicarboxylic acid (XIII) was methylated with diazomethane to form the methyl ester (XIV) and the ester was saponified with methanolic potassium hydroxide. The acid obtained on acidification of the saponification product showed the same melting point, and infrared and ultraviolet absorption spectra as those of the dicarboxylic acid (XIII) obtained by the ring cleavage of the coumarin compound (XII). The infrared spectrum of (XIV) did not show the absorption at 2.98 μ and, therefore, it is certain that it has no hydroxyl. It is also certain, from the following experiment, that saponification of the ester with methanolic potassium hydroxide did not cause demethylation of the methoxyl group. The methyl ester (XV), obtained by treatment of (XII) with diazomethane, was saponified with methanolic potassium hydroxide under the same conditions and the infrared spectrum of the carboxylic acid (XVI) obtained on acidification of the saponification product showed no absorption for hydroxyl at around 3.0 μ but exhibited absorptions at 3.75, 3.85, and 5.88 μ. From these data and ultraviolet absorption, (XVI) is known to be 6-oxo-3,4-dimethoxy-6,7.8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]-pyran-1-propionic acid. Since the methoxyl group is not likely to undergo demethylation by saponification with methanolic potassium hydroxide, the dicarboxylic acid (XIII) should not contain a phenolic hydroxyl group.

Analytical values of (XIII) indicate the presence of three methoxyls and absorption at 2.98 μ in this compound is considered to be that of a hydroxyl in one carboxylic acid. Similarly, the absorption at 5,73 μ is probably that of carbonyl shifted to a slightly longer wave-length region. It may be assumed that one of the COOH groups in this dicarboxylic acid (XIII) is present as a dimer and the other as a monomer, due probably to steric interference. This must be one of very rare examples.

The Dieckmann's intramolecular cyclization-condensation of the dicarboxylic acid

ester (XIV) by heating with potassium *tert*-butoxide in xylene, followed by saponification and decarboxylation afforded the ketone compound (III), which is also obtained on heating the free dicarboxylic acid (XIII) in acetic anhydride to effect dehydrative intramolecular cyclization-condensation and followed by decarboxylation. This dehydrative condensation product is obtained in about one-third the yield from the Dieckmann condensation. (III) forms an oxime, its infrared spectrum indicates the absorption for α,β-unsaturated carbonyl at 6.02 μ, and its ultraviolet spectrum has the absorption maxima at 240 and 302 mμ, suggesting the presence of conjugated double donds in the B- and C-rings. Consequently, (III) is considered to be 1,2,3-trimethoxy-5,6,9,10,11,12-hexahydrobenzo[*a*]heptalen-7(8*H*)-one. This fact shows that cyclization of the B-ring had been effected.

Since (III) was obtained from (XIV) by the Dieckmann condensation, the carbon atom in the alicyclic 1-position in (XIV) dose not take part in the reaction and there is an active methylene group adjacent to the side-chain carboxyl in the 6-position of the benzene ring in (XIV). This side chain is saturated and by retrospection, the side chain in (X) must be saturated and the conjugated double bond (s) must be in the coumarin ring, proving that the structure of (X) is a coumarin compound with saturated side chain.

Reduction of the oxime (XVII) of (III) with lithium aluminium hydride gave the 7-amino compound (XVIII), m.p. 98°, $[\alpha]_D$ 0°. Optical resolusion of this racemic compound with *d*-tartaric acid or *d*-camphorsulfonic acid did not materialize. The N-acetylated compound (XIX) of (XVIII) was also a racemate and must be *dl*-7-acetamido-1,2,3-trimethoxy-5,6,7,8,9,10,11,12-octahydrobenzo[*a*]heptalene.

The N-acetylated compound (XIX) was assumed to be identical with demethoxydeoxyhexahydrocolchicine, prepared from colchicine by the Rapoport's method,[6] but the infrared spectra of these two compounds failed to show similarity of absorption bands in the finger-print region longer than 6.3 μ, although the spectral curve agreed in the shorter wave-length region than 6.3 μ. (XIX) did not agree either with *dl*-demethoxydeoxyhexahydrocolchicine prepared by the method of Rapoport and others[6] from *dl*-cochicine obtained by the method of Corrodi and others.[7] Consequently, these compounds must have double bonds in different positions. Considering the route of synthesis of the N-acetylated compound (XIX), the position of its double bond must be at 7a～12a, while that in the compound synthesized by Rapoport and others[6] was assumed to be 7a～12a or 12～12a.*[2]

Lor 12-12a*[2]. ter, Muller and others[8] considered the position of this double bond to be at 7a～12a, carried out decomposition of colchicine and isocolchicine to prepare unsatur ated nitriles, and assumed from their ultraviolet absorption spectra that the structure of colchicine is a 9-methoxy-10-oxo compound. This was refuted by Fordes and others[9] who stated that if the double bond were assumed to be at 12～12a, this conclusion would be reversed and the accepted formula for colchicine showed no inconsistency. They suggested that the double bond must be at 12～12a. Later, Loewenthal and others[10] treated 1,2,3-trimethoxy-5,6,8,9,10,11,12a-octahydrobenzo[*a*]heptalene (A) with boron trifluoride to shift the double bond and obtained 1,2,3-trimethoxy-5,6,7,8,9,10,11,12-octahydrobenzo[*a*]heptalene (B), identifying the latter with demethoxydeoxydeacetamido-

*[2] Dr. Rapoport said, when he visited this laboratory in 1960, that he had received a letter which said that "the position of this double bond is more likely to be 12～12a from the measurement of NMR spectrum."

6) H. Rapoport, A.R. Williams, J.E. Campion, D.E, Pack: *Ibid.*, **76**, 3693 (1954); H .Rapoport, J.E. Campion J.E. Gordon: *Ibid.*, **77**, 2389 (1955).
7) H. Corrodi, E. Hardegger: Helv. Chim. Acte, **22**, 193 (1957).
8) G. Muller, L. Velluz: Bull. soc. chim. France, **1955**, 1452.
9) E.J. Fordes: Chem. & Ind. (London), **1956**, 192.
10) H.J.E. Loewenthal, P. Rona: Proc. Chem. Soc., **1958**, 114.

octahydrocolchicine. They stated that the position of the double bond would be determined by the NMR spectrum.

In the present series of work, the N-acetylated compound (XIX) was allowed to stand with boron trifluoride at a room temperature for a long period of time and a product (XX) of m.p. 185° was obtained. Its infrared and ultraviolet spectra agreed well with the levorotatory and racemic demethoxydeoxyhexahydrocolchicine, and there was no depression of the melting point on admixture of (XX) with the racemic compound. Since (XX) was obtained from the N-acetylated compound (XIX) under mild conditions, there could not have been any change in the ring and the side chain. Therefore, there must have been a shift of the double bond or the two are polymorphs but the difference of infrared and ultraviolet spectra of (XIX) and (XX) in solution makes polymorphism unlikely. Con-

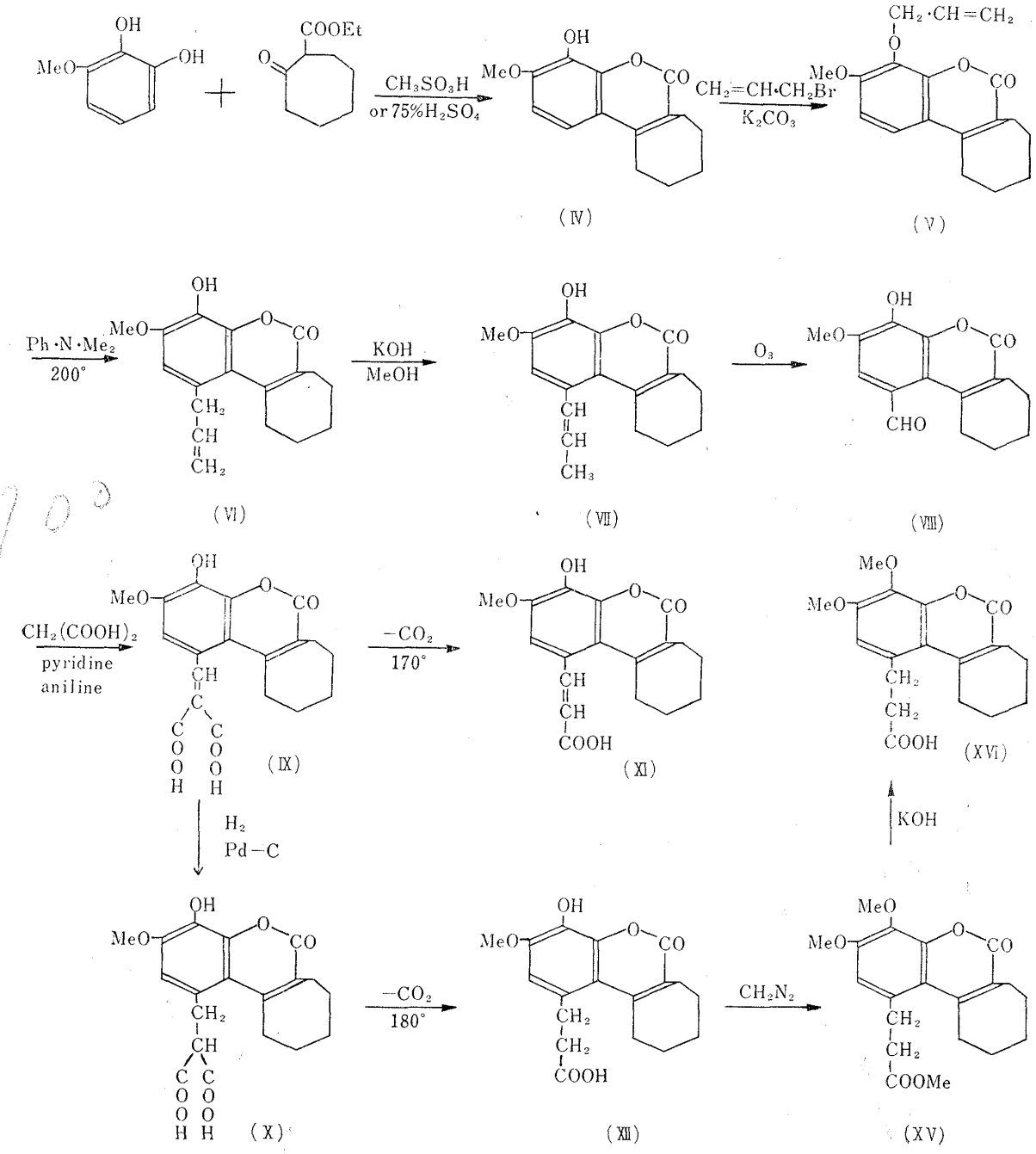
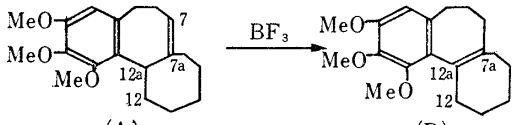


Chart 1. (1)

sequently, (XX) must be a compound in which the double bond has shifted to 12~12a positions. It follows, therefore, that the double bond in the demethoxydeoxyhexahydrocolchicine and demethoxydeoxydeacetamidoöctahydrocolchicine (B), which both was obtained from colchicine, described above must be at 12~12a, and these two compounds are respectively 7-acetamido-1, 2, 3-trimethoxy-5, 6, 7, 7a, 8, 9, 10, 11-octahydrobenzo[*a*]heptalene and 1,2,3-trimethoxy-5,6,7,7a,8,9,10,11-octahydrobenzo[*a*]heptalene.



The foregoing experiments show that total synthesis of demethoxydeoxyhexahydrocolchicine, one of the decomposition products of colchicine, had been effected and its structure determined.

The Leuckart reaction of the cyclic ketone compound (III) by the method of Horii

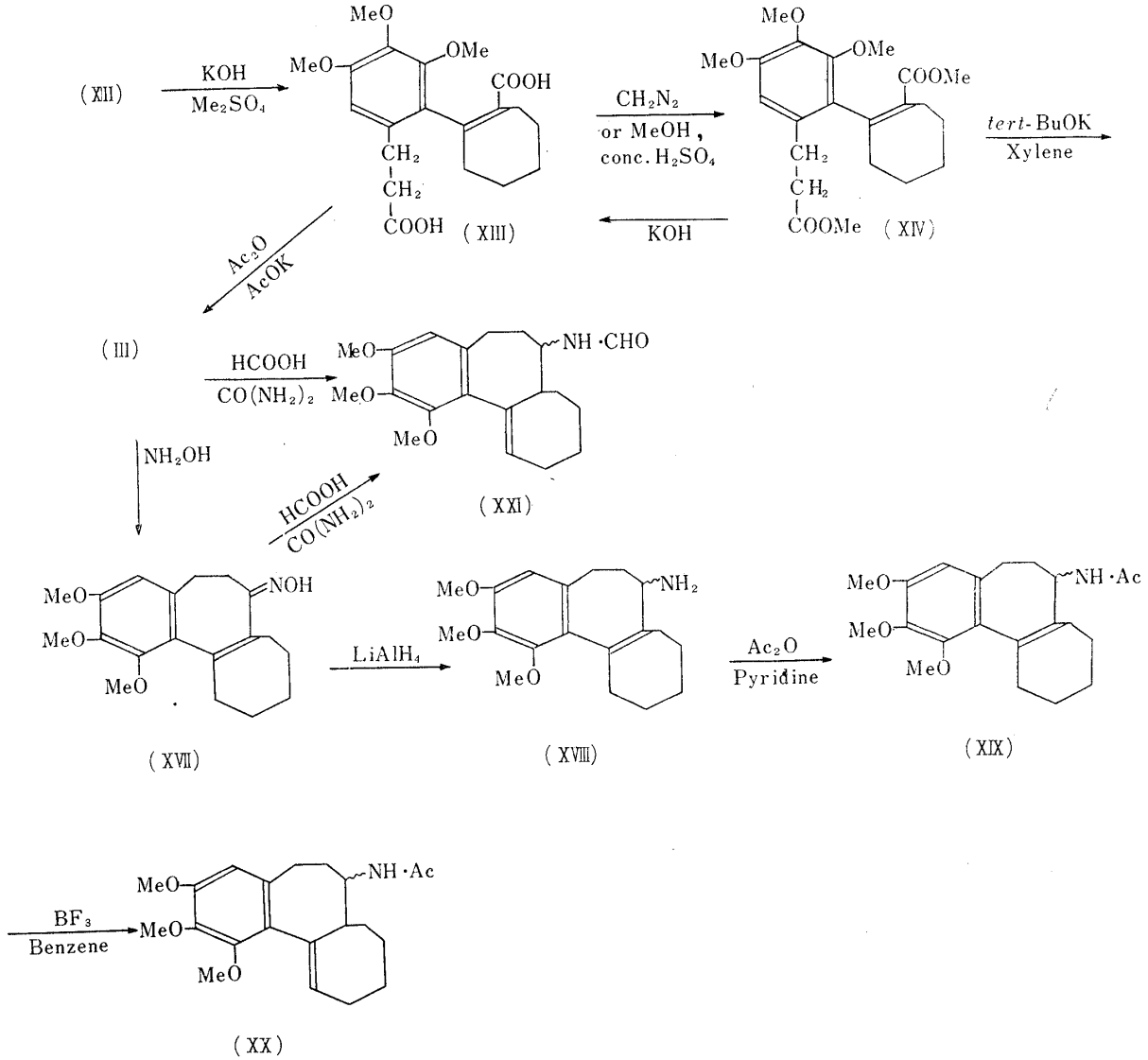


Chart 2. (2)

and others[11] gave the N-formylated compound (XXI) of m.p. 196°, whose infrared spectrum exhibited absorptions at 3.04 and 6.45 μ for NH and at 6.03 μ for NH-CO. The ultraviolet spectrum of (XXI) had absorption maximum of the same shape as that of the N-acetylated compound. Since the reaction conditions were rather drastic, such as 3 hours at 180° in formic acid, the double bond is assumed to be at 12~12a position and (XXI) may be considered as *dl*-7-formamido-1,2,3-trimethoxy-5,6,7,7a,8,9,10,11-octahydrobenzo-[*a*]heptalene. The infrared and ultraviolet absorption spectra of (XXI) in chloroform solution were completely identical with the infrared spectrum (in chloroform) and ultraviolet spectrum of N-formyldeactyldemethoxydeoxyhexahydrocolchiciceine, prepared by the method of Rapoport ane others[6] from the N-formyldeacetylcolchicine, obtained by the method of Šantavý and others.[12] The same N-formylated compound (XXI) was obtained by the use of the oxime (XVII) in place of the cyclic ketone compound (III).

Experimental*3

3-Methoxy-4-hydroxy-8,9,10,11-tetrahydrobenzo[*b*]cyclohepta[*d*]pyrnan-6(7*H*)-one (IV)——A solution of 24.7 g. of 1-O-methylpyrogallol[13] and 32.5 g. of ethyl 2-oxocycloheptanecarboxylate[14] dissolved in 74 cc. $MeHSO_3$ was treated in the same way as for the preparation of (VIII) described in Part I of this series,[1] and 45 g. of powdery product was obtained. This was recrystallized from EtOH to 33.75 g. (75%) of prisms, m.p. 176.5°. Use of 75% (v/v) of H_2SO_4 in place of $MeHSO_3$ resulted in 56% yield. *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.17; H, 6.21. IR λ_{max}^{Nujol} μ 3.00 (OH), 5.92 (coumarin-CO). UV λ_{max}^{EtOH} mμ (log ε): 258~264 (3.96), 320 (4,17).

3-Methoxy-4-allyloxy-8,9,10,11-tetrahydrobenzo[*b*]cyclohepta[*d*]pyran-6(7*H*)-one (V)——From 45.9 g. of crude (IV), 39.2 cc. of allyl bromide, 31,2 g. of K_2CO_3, 2.61 g. of NaI, 600 cc. of MeOH, and 257 cc. of H_2O, 48 g. of liquid product was obtained by the same method as for the preparation of (IX) in Part I.[1] This was passed throurh a column of alumina, the column was washed with 400 cc. of a mixture (3:1) of petr. ether and benzene, and eluted with 1.5 L. of benzene and 500 cc. of 0.5% EtOH-benzene mixture. Evaporation of the solvent from the eluate left 38 g. (71.2%) of a liquid which was allowed to stand under refrigeration. The white needle crystals that separated out were washed with Et_2O and dried to obtain needles, m.p. 6.5 *Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.91. IR λ_{max}^{Nujol} μ: 5.83 (coumarin-CO). 10.15, 10.73 (allyl), 12.43 (adjacent CH_2). UV λ_{max}^{EtOH} mμ (log ε): 242 (3.71), 251 (3.72), 260 (3.69), 322 (4.19).

1-Allyl-3-methoxy-4-hydroxy-8,9,10,11-tetrahydrobenzo[*b*]cyclohepta[*d*]pyran-6(7*H*)-one (VI)——From 1.835 g. of (V) and 3.6 cc. of N,N-dimethylaniline, the product was obtained in the same way as for the preparation of (X) in Part I,[1] and it was recrystallized from AcOEt to 1.549 g. (84.5%) of crystals melting at 166°. *Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.91; H, 6.91. IR λ_{max}^{Nujol} μ: 2.92 (OH), 5.93 (coumarin-CO), 9.87, 10.96 (allyl), 11.63 (isolated CH). UV λ_{max}^{EtOH} mμ (log ε): 267 (4.01), 328 (4.12).

1-Propenyl-3-methoxy-4-hydroxy-8,9,10,11-tetrahydrobenzo[*b*]cyclohepta[*d*]pyran-6(7*H*)-one (VII)——From 87 g. of KOH, 260 cc. of MeOH, and 29 g. of (VI), the product was obtained by the same way as for the preparation of (XI) in Part I,[1] and recrystallized from a mixture of AcOEt and CH_2Cl_2 to pale yellow needles, m.p. 175°. Yield, 24.02 g. (80%). *Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.98; H, 6.85. IR λ_{max}^{Nujol} μ: 3.00 (OH), 5.90 (coumarin CO), 1.034 (propenyl). UV λ_{max}^{EtOH} mμ (log ε): 220 (4.52), 260 (4.17), 332 (4.19).

1-Formyl-3-methoxy-4-hydroxy-8,9,10,11-tetrahydrobenzo[*b*]cyclohepta[*d*]pyran-6(7*H*)-one (VIII)——Into a solution of 14.7 g. of (VII) dissolved in 735 cc. of CH_2Cl_2, 0.45 g. (1.04 moles) of O_3 was passed for 1 hr. at −60°, the ozonide was decomposed with 20% $NaHSO_3$ solution, and CH_2Cl_2 solution was separated. This solution was washed with water and CH_2Cl_2 was evaporated to leave 12.7 g. (90%) of a product which was recrystallized from CH_2Cl_2 to yellow needles, m.p. 227°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.72; H, 5.88. IR λ_{max}^{Nujol} μ: 3.00 (OH), 5.85 (coumarin CO), 6.01 (CHO). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.13), 280 (3.88), 348 (3.97).

α-Carboxy-3-methoxy-4-hydroxy-6-oxo-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-1-acrylic Acid (IX)——By the same procedure as for the preparation of (XIV) in Part I,[1] the product

*3 All m.p.s are uncorrected.

11) Z. Horii, Y. Tamura, Y. Murakami: Yakugaku Zasshi, **72**, 1206 (1952).

12) Fr. Šantavý, T. Reichstein: Helv. Chim. Acta, **33**, 1606 (1950).

13) Org. Syntheses. **26**, 90 (1946).

14) V. Prelog, W. Hinden: Helv. Chim. Acta, **27**, 1854 (1944).

was obtained from 24.3 g. of (Ⅷ), 17.6 g. of malonic acid, 200 cc. of pyridine, and 8.56 cc. of aniline and recrystallized from hydr. MeOH to 21.3 g. (43.7%) of yellow needles, m.p. 252° (decomp.). *Anal.* Calcd. for $C_{19}H_{18}O_8$: C, 60.96 H, 4.85. Found: C, 60.86; H, 4.81. IR λ_{max}^{Nujol} μ: 2.93 (OH), 3.7~4.0 (OH in COOH), 5.76 (CO in COOH), 5.88 (CO in C=C-COOH), 6.00 (coumarin CO). UV λ_{max}^{EtOH} mμ (log ε): 229 (4.22), 254 (4.19), 300 (3.98), 346 (4.20).

α-Carboxy-3-methoxy-4-hydroxy-6-oxo-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-1-propionic Acid (X)——From 33.1 g. of (Ⅸ), 15 g. of 5% Pd-C, and 450 cc. of MeOH, the product was obtained by the same method as for the preparation of (Ⅹ) in Part I[1], and recrystallized from MeOH to 28.6 g. (86%) of needles, m.p. 255°. *Anal.* Calcd. for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36; COOH, 23.92. Found: C, 60.56; H, 5.49; COOH, 24.06. IR λ_{max}^{Nujol} μ: 2.95 (OH), 3.7~3.9 (COOH), 5.74, 5.82 (CO in COOH), 6.05 (coumarin CO), UV λ_{max}^{EtOH} mμ (log ε): 264~268 (4.05), 328 (4.16).

3-Methoxy-4-hydroxy-6-oxo-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-1-acrylic Acid (XI)——One gram of (Ⅸ) was heated at 170° for 7 hr. at a reduced pressure of 1 mm. Hg to effect decarboxylation, cooled, dissolved in a solution of 2 g. of $NaHCO_3$ in 100 cc. of H_2O, and the solution was filtered. The filtrate was acidified, the precipitate was collected, washed with H_2O, and dried to 0.7 g. of a product which was recrystallized from MeOH to 0.5 g. (56%) of yellow needles, m.p. 255° (decomp.). *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.12; H, 5.38. IR λ_{max}^{Nujol} μ: 3.03 (OH), 3.7~3.9 (COOH), 5.90 (CO in C=C-COOH), 6.05 (coumarin CO), 10.28 (-C(H)=C(H)-). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.30), 263 (4.21), 290 (4.01), 344 (4.09).

3-Methoxy-4-hydroxy-6-oxo-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-1-propionic Acid (XII)——To effect decarboxylation, 28.6 g. of (Ⅹ) was heated at 180° for 8 hr. at a reduced pressure of 1 mm. Hg, 25.25 g. residue was dissolved in a solution of 75 g. of $NaHCO_3$ in 3 L. of water, and the solution was filtered. After treatment of the filtrate with activated charcoal, the filtrate was acidified, and the precipitate was collected. Recrystallization from hydrous MeOH gave 25 g. (99%) of white needles, m.p. 248° (decomp.). *Anal.* Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.95; H, 6.00. IR λ_{max}^{Nujol} μ: 2.96 (OH), 3.7~4.0 (COOH), 5.78 (CO in COOH), 6.05 (coumarin CO), UV λ_{max}^{EtOH} mμ (log ε): 264~267 (4.04), 328 (4.14).

2-[6-(2-Carboxyethyl)-2,3,4-trimethoxyphenyl]-1-cycloheptenecarboxylic Acid (XIII)——From 24.8 g. of (Ⅻ), 500 cc. of Me_2SO_4, and 2.5 L. of 20% KOH solution, 26.3 g. of (XIII) was obtained by the same process as for the preparation of (Ⅴ) in Part I, and this was recrystallized from AcOEt to 21.9 g. (77.5%) of white rhombic crystals, m.p. 141°.

A mixture of 306 mg. of the methyl ester (XIV) of (XIII), 0.5 g. of KOH, and 10 cc. of 90% MeOH was boiled for 2 hr. to effect saponification, the solvent was evaporated from this mixture, and mixture was acidified. This was extracted with AcOEt, the extract was washed with H_2O, and AcOEt was evaporated. Recrystallization of its residue from AcOEt gave (XIII) as rhombic crystals, m.p. 141°. *Anal.* Calcd. for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93; CH_3O, 24.60. Found: C, 63.52; H, 7.00; CH_3O, 24.30. IR λ_{max}^{Nujol} μ: 2.98 (OH in COOH), 3.7~4.0 (COOH), 5.73 (COOH), 5.95 (CO in C=C-COOH). IR $\lambda_{max}^{CHCl_3}$ μ: 3.75, 3.90 (COOH), 5.90 (CO in C=C-COOH). UV: λ_{max}^{EtOH} 270 mμ (log ε 3.44).

Methyl 2-[6-(2-Methoxycarbonylethyl)-2,3,4-trimethoxyphenyl]-1-cycloheptenecarboxylate (XIV)——A solution of 21.9 g. of (XIII) dissolved in a mixture of 60 cc. each of MeOH and Et_2O was treated with CH_2N_2, as in the preparation of (XIX) in Part I, and 23.8 g. of the ester was obtained as a pale yellow liquid. Molecular distillation of this product gave a colorless liquid, b.$p_{0.001}$ 210° (bath temp.). *Anal.* Calcd. for $C_{20}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.37; H, 7.67. IR $\lambda_{max}^{liq.}$ μ: 5.74 (ester-CO), 5.84 (CO in C=C-COOR). UV: λ_{max}^{EtOH} 275 mμ (log ε 3.58).

A mixture of 225 mg. of (XIII), 10 cc. of MeOH, and 0.1 cc. of conc. H_2SO_4 was treated as above and 230 mg. (95.2%) of a liquid was obtained, whose infrared and ultraviolet spectra were the same as the above data.

Methyl 3,4-Dimethoxy-6-oxo-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-1-propionate (XV)——A solution of 3.3 g. of (Ⅻ) dissolved in a mixture of MeOH and Et_2O was treated with CH_2N_2, Et_2O solution was washed with 1% KOH solution and water, and Et_2O was evaporated. White pris-matic crystals thereby obtained were washed with Et_2O and dried to 3.6 g. (100%) of crystals melting at 143°. *Anal.* Calcd. fro $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.77; H, 6.66. IR λ_{max}^{Nujol} μ: 5.76 (ester-CO), 5.89 (coumarin-CO), UV λ_{max}^{EtOH} mμ (log ε): 246 (3.85), 254 (3.86), 262 (3.82), 328 (4.18).

3,4-Dimethoxy-6-oxo-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-1-propionic Acid (XVI)——A solution of 39 mg. of (XV) and 0.5 g. of KOH dissolved in a mixture of 1 cc. of H_2O and 9 cc. of MeOH was boiled for 2 hr., the solvent was distilled off, the residue was acidified, and extracted with AcOEt. The extract was washed with water, AcOEt was evaporated, and the residue was recrystallized from AcOEt and petr. ether to white dendritic crystals, m.p. 191°. Yield, 36 mg. (100%). *Anal.* Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.98; H, 6.48. IR λ_{max}^{Nujol} μ: 3.75,

3.85 (OH in COOH), 5.88 (CO in COOH), 5.91 (coumarin-CO). UV λ_{max}^{EtOH} mμ (log ε): 245 (3.87), 251 (3.96), 251 (3.86), 262 (3.81), 326 (4.16).

1,2,3-Trimethoxy-5,6,9,10,11,12-hexahydrobenzo[*a*]heptalen-7(8*H*)-one (III)——a) From 100 cc. of xylene solution of 23.5 g. of (XIV) and 800 cc. of xylene solution of tert-BuOK, prepared from 8 g. of K, 100 cc. of tert-BuOH, and 300 cc. of xylene, 16.2 g. of a neutral substance was obtained by the same procedure as for the preparation of (XX), (a), in Part I. This product was passed through a column of 250 g. of alumina, the column was washed with 500 cc. of a mixture (1:1) of petr. ether and benzene, and eluted with 500 cc. of the same mixture and 1 L. of benzene. The residue obtained from the eluate was recrystallized from MeOH to prisms, m.p. 107°. Yield, 5.58 g. (30.5%). *Anal.* Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.74; H, 8.05. IR λ_{max}^{Nujol} μ: 6.02 (conjugated CO), 6.18 (C=C). UV λ_{max}^{EtOH} mμ (log ε): 240 (4.23), 302 (3.71).

b) From 3.04 g. of (XIII), 200 cc. of Ac_2O, and 6 g. of AcOK, ca. 1.1 g. of an oily product was obtained by the same procedure as for the preparation of (XX), (b) in Part I. This product was passed through 17 g. of almina, the column of washed with 34 cc. of a mixture (1:1) of petr. ether and benzene, and eluted with 51 cc. of the same mixture and 70 cc. of benzene. Evaporation of the solvent from the eluate gave 914 mg. of a yellow oil. Recrystallization from MeOH gave 272 mg. (10.7%) of colorless prisms, m.p. 107~109°, undepressed on adimixture with the product of m.p. 107°, obtained by the foregoing method (a).

1,2,3-Trimethoxy-5,6,9,10,11,12-hexahydrobenzo[*a*]heptalen-7(8*H*)-one Oxime (XVII)——A mixture of 4.8 g. of (III) and 6 g. of $NH_2OH \cdot HCl$ dissolved in a mixture of 7 cc. of pyridine and 60 cc. of dehyd. EtOH was boiled for 20 hr. The reaction mixture was shaken with H_2O and benzene, the benzene layer was washed consecutively with H_2O, 5% HCl, and H_2O, and dried. The residue obtained on evaporation of benzene was recrystallized from MeOH to white prisms, m.p. 154°. Yield, 5.03 g. (100%). *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68:86; H, 7.60; N, 4.23. Found: C, 68.66; H, 7.34; N, 4.51. IR λ_{max}^{Nujol} μ: 3.10 (N-OH), 6.13 (C=N), 10.48 (NO). UV: λ_{max}^{EtOH} 267 mμ (log ε 3.98).

***dl*-7-Amino-1,2,3-trimethoxy-5,6,7,8,9,10,11,12-octahydrobenzo[*a*]heptalene (XVIII)**——A solution of 3.31 g. of (XVII) dissolved in 30 cc. of tetrahydrofuran was added dropwise into a solution of 0.4 g. (1.05 mole) of $LiAlH_4$ dissolved in 20 cc. of tetrahydrofuran and the mixture was boiled for 6 hr. The product was decomposed with ice water, ane solution was acidified, and extracted with Et_2O. The aqueous solution was basified and extracted with Et_2O. Both Et_2O extracts were combined, Et_2O was evaporated, and the residue was diluted with 5% NaOH solution. This solution was extracted with Et_2O, Et_2O extract was washed with water, and dried. Evaporation of Et_2O left 1.297 g. of a product which was recrystallized from Et_2O to 320 mg. of prisms, m.p. 98°. *Anal.* Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.69; H, 8.46; N, 4.63. IR λ_{max}^{Nujol} μ: 2.92, 3.00 (NH), UV λ_{max}^{EtOH} mμ (log ε): 218 (4.35), 255 (4.02). $[\alpha]_D^{26}$ 0° (c=0.4, EtOH).

A solution of 320 mg. of (XVIII) and 75 mg. of *d*-tartaric acid dissolved in MeOH was allowed to stand and needle crystals that separated out were recrystallized from MeOH to 391 mg. of prisms, m.p. 212°. Its analytical values indicated it to be a neutral substance. *Anal.* Calcd. for $C_{42}H_{60}O_{12}N_2$: C, 64.26; H, 7.70; N, 3.57. Found: C, 64.41; H, 7.66; N, 3.31. IR λ_{max}^{Nujol} μ: 2.80, 2.85 (OH), 3.80, 3.95 (COOH), 4.60 (NH_3^+), 6.43 (COO^-), 8.92 (COH), UV λ_{max}^{EtOH} mμ (log ε): 218 (4.62), 256 (4.29). $[\alpha]_D^{27}$ 0° (c=2.20, H_2O).

***dl*--Acetamido-1,2,3-trimethoxy-5,6,7,8,9,10,11,12-octahydrobenzo[*a*]heptalene (XIX)**——A solution of 95 mg. of (XVIII) and 1 cc. of Ac_2O dissolved in 2 cc. of pyridine was allowed to stand for 12 hr. at room temperature, Ac_2O and pyridine were distilled off below 20°, and the residue was dissolved in benzene. The benzene solution was washed consecutively with 5% HCl, H_2O, 5% KOH, and H_2O, dried, and the solvent was evaporated. The residue was passed through a column of 2 g. of alumina, and the column was eluted with a mixture of 0.5% EtOH and benzene, from which 113 mg. of needle crystals was obtained. Recrystallization from a mixture of AcOEt and petr. ether afforded needles, m.p. 155°. *Anal.* Calcd. for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 69.90; H, 8.15; N, 3.96. IR $\lambda_{max}^{CHCl_3}$ μ: 2.85, 2.96 (NH), 6.02, 6.65 (NH-CO), UV λ_{max}^{EtOH} mμ (log ε): 222 (4.43), 256 (4.09).

***dl*-7-Acetamido-1,2,3-trimethoxy-5,6,7,7a,8,9,10,11-octahydrobenzo[*a*]heptalene (XX)**——A solution of 469 mg. of (XIX) dissolved in a mixture of 0.26 cc. of $BF_3 \cdot 2Et_2O$ and 26 cc. of dehyd. benzene was allowed to stand for 60 hr. at room temperature. The mixture was diluted with H_2O, the benzene layer was washed with H_2O, 5% KOH, and H_2O, dried and the solvent was evaporated, leaving 470 mg. of a product, This residue was adsorbed on 9.4 g. of alumina which was washed with 659 cc. of benzene and eluted with 188 cc. of a mixture of 0.5% EtOH and benzene. Evaporation of the solvent from the eluate gave 250 mg. of a residue which was recrystallized from AcOEt to 167 mg. of white needles, m.p. 185°. *Anal.* Calcd. for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.22; H, 7.82; N, 4.09. IR $\lambda_{max}^{CHCl_3}$ μ: 2.83, 2.94, 3.34, 3.43, 3.54, 6.02, 6.38, 6.40, 6.65, 6.73, 6.90, 7.12, 7.32, 7.42, 7.58, 7.72, 7.80, 7.90, 8.78, 9.05, 9.63, 9.92, 10.13, 10.35, 10.64, 10.88, 11.84. UV λ_{max}^{EtOH} mμ (log ε): 220 (4.42), 254 (4.14).

***dl*-7-Formamido-1,2,3-trimethoxy-5,6,7,7a,8,9,10,11-octahydrobenzo[*a*]heptalene (XXI)**——A mix-

ture of 395 mg. of (III), 2.4 g. of HCOOH, and 1.2 g. of $CO(NH_2)_2$ was heated in N_2 stream at 110~120° for 2 hr., at 120~180° for 1 hr., and at 180° for 3 hr. After cool, the mixture was diluted with water and extracted with benzene. The benzene solution was washed consecutively with 4% NaOH, 5% HCl, and H_2O, and evaporation of the solvent left 130 mg. of a product. This was adsorbed on 2.6 g. of alumina which was eluted with 180 cc. of benzene and 50 cc. of a mixture of 0.5% EtOH and benzene, from which 64 mg. of a powdery product was obtained. This was recrystallized from Et_2O to 13.2 mg. of white needles, m.p. 196°. *Anal.* Calcd. for $C_{20}H_{27}O_4N$: C, 69.54; H, 7.88; N, 4.06. Found : C, 69.51; H, 7.66; N, 4.08. IR λ_{max}^{KBr} μ : 3.04 (NH), 6.03 (NH-CO), 6.45 (NH). UV λ_{max}^{EtOH} mμ (log ε) : 220 (4.44), 254 (4.14). IR $\lambda_{max}^{CHCl_3}$ μ : 2.90, 3.34, 3.42, 3.51, 5.92, 6.25, 6.40, 6.72, 6.81, 6.86, 6.97, 7.11, 7.16, 7.32, 7.40, 7.43, 7.57, 7.72, 7.81, 7.92, 8.10, 8.39, 8.82, 9.09, 9.70, 10.04, 10.22, 10.41, 10.65, 10.84, 11.92.

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Summary

Demethoxydeoxyhexahydrocolchlicine (XX), one of the decomposition products of colchicine was synthesized. 1-O-Methylpyrogallol was derived to 3-methoxyl-4-hydroxy-8,9,10,11-tetrahydrobenzo[*b*]cyclohepta[*d*]pyran-6-one (IV) and to methyl 2-[6-(2-methoxycarbonylethyl)-2,3,4-trimethoxyphenyl]-1-cycloheptenecarboxylate (XIV) via the 1-formyl compound (VIII) and 1-(2-carboxyethyl) compound (XII) of (VI), and Dieckmann condensation of (XIV) gave 1,2,3-trimethoxy-5,6,10,12-hexahydrobenzo[*a*]heptalen-7(8*H*)-one, which was also obtained by dehydrative condensation of the free acid (XIII) of (XIV). (III) was derived to its oxime which was reduced and acetylated to *dl*-7-acetamido-1,2,3-trimethoxy-5,6,7,8,9,10,11,12-octahydrobenzo[*a*]heptalene (XIX) whose double bond was rearranged to form the racemic compound of (XX). The position of the double bond in (XX) was determined. *dl*-N-formyldeacetyldemethoxydeoxyhexahydrocolchicine (XXI) was obtained in one step from (III) by the Leuckart reaction.

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46. **Takahiro Nakamura** : Studies on the Total Synthesis of *dl*-Colchiceine. III.[1]

(*Takamine Laboratory, Sankyo Co., Lte.*[*1])

As reported in the preceding paper,[1] *dl*-demethoxydeoxyhexahydrocolchicine (I) was synthesized as an intermediate for a total synthesis of colchicine. The levorotatory compound of (I) had been obtained from colchicine by the method of Rapoport and others.[2] In order to introduce further double bond into the C-ring of (I) to form the tropilidene ring, the levorotatory compound of (I) was submitted to dehydrogenation reaction with selenium dioxide and mercuric acetate but the reaction did not materialize. Dryden and

*1 Nishi-Shinagawa, Shinagawa-ku, Tokyo (中村隆洋).

1) Part II : This Bulletin, **10**, 291 (1962).

2) H. Rapoport, A. R. Williams, J. E. Campion, D. E. Pack : J. Am. Chem. Soc., **76**, 3693 (1954).